ANTIPLATELET AGENTS

MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

Antiplatelet agents are used in ischemic cerebrovascular disease. Antiplatelet therapy reduces vascular morbidity and mortality 27% among patients with cardiovascular disease who are at high risk for recurrent illness.[1] Medications used for secondary prevention of stroke include: aspirin, dipyridamole, ticlopidine, clopidogrel and the dipyridamole/aspirin combination.

Aspirin is currently the standard of care for stroke prevention in patients with identified atherothrombotic disease.[2] Ticlopidine is available as alternative therapy, but serious side effects such as neutropenia limit its usefulness. Clopidogrel, a new thienopyridine derivative similar to ticlopidine, reduces the risk of stroke 7.3% over aspirin (p=NS).[3] Because of high drug cost, clopidogrel should be reserved for patients who fail aspirin or cannot tolerate it. Long term safety data for clopidogrel are limited to 3 years where as aspirin has been used for more than 100 years.[4] The combination of dipyridamole and aspirin reduced the risk of stroke by 37% compared with aspirin alone (22%) and dipyridamole alone (24%).[5] No head to head trials compare ticlopidine, clopidogrel, dipyridamole/aspirin, or warfarin in patients who fail aspirin monotherapy.

Prevention of cerebrovascular disease is the most important aspect of therapeutic management. Control of hypertension, hyperlipidemia, obesity, tobacco use, and alcohol use is essential to the overall care of the patient with cerebrovascular disease. The role of aspirin in primary prevention of stroke is uncertain. The National Stroke Association has developed evidence-based consensus guidelines on the prevention of first stroke. These recommendations are provided in Table 1.[6]

Table 1. Guidelines for prevention of first stroke[6]

Condition	Recommendation
Hypertension	Follow JNC VI Guidelines for lifestyle modification, initiation of specific therapy and multidisciplinary management strategies.[7]
Myocardial Infarction	Aspirin therapy or warfarin in patients with atrial fibrillation, left ventricular thrombus or significant left ventricular dysfunction, and statin agents if high lipid levels.
Atrial fibrillation	Warfarin or aspirin therapy, depending on age and risk factors.
Diabetes mellitus	Follow American Diabetes Association recommendations for control of diabetes.
Hyperlipidemia	Follow NCEP guidelines for dietary and pharmacological management with hyperlipidemia or atherosclerotic disease.[8]
Asymptomatic carotid stenosis of > 60%	Evaluate for carotid endarterectomy when surgical morbidity and mortality is < 3%.
Lifestyle factors	Modification of smoking, alcohol consumption, physical activity and diet.

Aspirin reduces the risk of stroke about 25%.[1] Although aspirin has only a modest effect, it is widely applicable and accessible, inexpensive, and relatively safe. Aspirin inhibits platelet aggregation by irreversible inactivation of cyclooxygenase, which in platelets prevents conversion of arachidonic acid to thromboxane A_2, a powerful vasoconstrictor and stimulator of platelet aggregation. Aspirin also inhibits prostacyclin (PGI_2) activity in the smooth muscle of vascular walls. PGI_2 inhibits platelet aggregation. This effect of aspirin is dose and duration related; the lower the aspirin dose the less effect on prostacyclin.[9]

The optimal dose of aspirin is controversial. Two randomized trials directly compared different aspirin doses in patients with transient ischemic attacks (TIAs) and minor stroke (1200 versus 300 mg/d and 283 versus 30 mg/day) and found no statistically significant differences.[10,11] The aspirin carotid endarterectomy (ACE) study

compared low dose aspirin (81 or 325 mg/d) to high dose aspirin (650 or 1300 mg/d) in 2849 patients after carotid endarterectomy.[12] The event rate of stroke, myocardial infarction or death within 3 months was lower in those assigned the lower aspirin dose ($p<0.03$). There was no significant effect on stroke alone. The executive summary from the FDA recommends low-dose aspirin (50 to 325 mg daily) for the prevention of stroke.[13] These recommendations are based on results from the Swedish Aspirin Low Dose Trial, the Second European Stroke Prevention Trial, and the United Kingdom Transient Ischemic Attack Aspirin Trial.[10,14,15]

Common side effects of aspirin include gastrointestinal irritation or ulceration, anaphylaxis, bronchospasm, and decreased renal function. The gastrointestinal toxicity of aspirin is dose related but even low dose aspirin slightly increases the risk of major bleeding.[9] For those unable to tolerate aspirin 325 mg/day because of minor dyspepsia, the options include taking aspirin with meals, using an enteric-coated formulation or taking a lower dose. For patients who experience an initial or recurrent TIA while taking aspirin, there is no evidence that increasing the dose of aspirin or changing to another antiplatelet agent will reduce the risk of subsequent stroke.[2]

The thienopyridines, ticlopidine and clopidogrel, inhibit platelet aggregation by inhibiting the adenosine diphosphate pathway for platelet activation.[16,17] They do not inhibit cyclooxygenase and formation of prothrombotic thromboxane and antithrombotic prostacyclin, as aspirin does. Clopidogrel is 50 to 100 times as potent as ticlopidine in inhibiting thrombosis and prolonging bleeding time. It takes 7 to 10 days for platelet function to return to normal after exposure to aspirin, ticlopidine, and clopidogrel; this time course corresponds to the life span of the circulating platelet.[18]

Clopidogrel 75 mg per day was compared to aspirin 325 mg per day in 19,185 patients with recent ischemic stroke or myocardial infarction or patients who had symptomatic atherosclerotic peripheral arterial disease.[3] The primary outcome was first occurrence of ischemic stroke, myocardial infarction, or death. Clopidogrel reduced the risk of the primary outcome occurring by 8.7% ($p=0.043$). For patients in the stroke subgroup, the relative risk reduction was 7.3% ($p=0.26$). Compared with aspirin, clopidogrel had a smaller relative risk reduction for stroke than ticlopidine (7.3% vs. 21%).[3,19] The side effect profile of clopidogrel is similar to aspirin.

Ticlopidine 250 mg bid was compared to aspirin 650 mg bid in 3069 patients with a recent TIA or minor stroke.[19] According to an intention to treat analysis, the overall risk reduction of fatal and nonfatal stroke by ticlopidine at 3 years was 21%. A subgroup analysis of this study showed that ticlopidine was particularly effective in patients who had been taking aspirin or anticoagulant therapy at the time of cerebral ischemic event. Other studies comparing aspirin to ticlopidine favored ticlopidine by 10%; however the results were not statistically significant.

Adverse reactions of ticlopidine include changes in liver enzymes, diarrhea, dyspepsia, abdominal cramps, nausea, and anorexia.[17] Reducing the dose may lessen the diarrhea and taking the medication with meals reduces other gastrointestinal symptoms. Severe neutropenia, thrombocytopenia, aplastic anemia, and thrombotic thrombocytopenic purpura have been reported with ticlopidine. The incidence of severe neutropenia with clopidogrel is similar to that with aspirin (0.04% vs. 0.02%) and less than that reported with ticlopidine (0.8%).[3,18] The neutropenia appears 27 to 60 days after starting therapy and is probably secondary to an arrested maturation of bone marrow myeloid precursors due to either a toxic or hypersensitivity reaction. The neutrophil count normalizes 4 to 21 days after stopping the drug.[19] Due to the adverse effect profile, ticlopidine should not be used as a first-line agent for stroke prevention.

Dipyridamole is a vasodilator which also exhibits antiplatelet effects. Dipyridamole inhibits platelet aggregation by interfering with the products of arachidonic acid metabolism, specifically thromboxane A_2 and prostacyclin PGI_2. Dipyridamole inhibits phosphodiesterase to increase levels of cyclic AMP in the platelet. This potentiates the platelet de-aggregating effect of prostacyclin. Dipyridamole also inhibits erythrocyte uptake of adenosine and adenosine metabolism. Common adverse effects of dipyridamole include: diarrhea, dizziness, lightheadedness and headache, exacerbation of angina pectoris, and blood pressure lability.[20] Dipyridamole alone is not effective for preventing stroke or other types of thrombosis.[21] It has generally been studied in combination

with other agents like aspirin or warfarin. Dipyridamole alone should not be used as a first-line agent for stroke prevention.

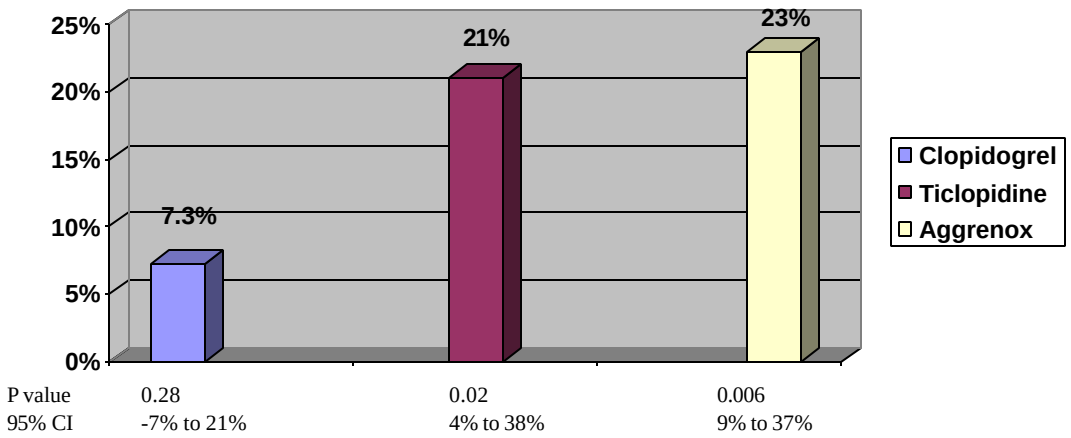
The combination product Aggrenox® (dipyridamole extended-release 75 mg and aspirin 25 mg) was recently marketed. Fourteen trials have compared the combination of dipyridamole and aspirin versus aspirin alone.[1,22] The doses commonly used were aspirin 900 to 1300 mg per day and dipyridamole 150 to 300 mg/day. No significant differences were found between the groups. For vascular events (nonfatal stroke, nonfatal MI, or vascular death), there was a trend favoring aspirin alone and for nonfatal stroke there was a trend favoring the combination.

The most recent trial (ESPS-2) was a two-year, randomized, double-blind trial in 6602 patients who had a TIA or completed ischemic stroke.[15] Aspirin 25 mg bid, extended release dipyridamole alone 200 mg bid, or the combination of the two agents were compared. This is the only trial evaluating the marketed dose of Aggrenox®. Endpoints for the study were: stroke, death, and stroke or death. Dipyridamole plus aspirin reduced the risk of stroke by 23% over aspirin alone. Although the results are promising, controversy has surrounded this study. The original publication was rejected by Lancet due to ethical concerns and one investigator was charged with falsifying and creating data.[22] Four hundred thirty eight patients from one center were excluded from data analysis.

The most common adverse reactions reported with Aggenox® include headache, diarrhea, and dizziness. The incidence of bleeding at any site was 8.7% with the combination versus 8.2% with aspirin monotherapy.[15] In the ESPS-2 trial, one in four patients randomized to either dipyridamole or Aggrenox® withdrew from the study.

Because earlier trials comparing aspirin alone to aspirin plus dipyridamole showed no difference between the groups and the limitations of the ESPS-2 study, the combination cannot currently be recommended as first line therapy for stroke prevention.

Figure 1. Relative Risk Reduction over Aspirin for Stroke



In conclusion, aspirin is the drug of choice for stroke prevention. For patients who do not tolerate aspirin, clopidogrel would be an alternative. For patients who experience a recurrent TIA while taking aspirin, there is no evidence that changing to another antiplatelet agent will reduce the risk of subsequent stroke. The role of Aggrenox® in stroke prevention is not well defined. Some practitioners may prefer to switch patients to Aggrenox® if the patient has had a subsequent stroke on aspirin, but there is no evidence to support this action.

Table 2. Antiplatelet agents- usual and maximum dosage [16,17,20,24]

Drug	Dosage Form(s)	Usual Dose for Stroke Prevention	Maximum Daily Dose for Stroke Prevention
Aspirin	Enteric coated tablets: 81 mg, 165 mg, 325 mg, 500 mg, 650 mg, 975 mg. Chewable tablets: 81 mg. Tablets: 325 mg, 500 mg. Extended release 650 mg. Controlled release 800 mg. Delayed release tablet: 81 mg. Suppositories 120 mg, 200 mg, 300 mg, and 600 mg. Buffered aspirin 325 mg, 500 mg.	81 mg/d to 325 mg/d	1300 mg per day- higher doses of aspirin are not superior to lower doses. For patients who experience an initial or recurrent TIA while taking aspirin, there is no evidence to support increasing the dose.
Clopidogrel (Plavix®)	Tablets: 75 mg	75 mg once daily	75 mg once daily- higher doses do not result in further platelet impairment.
Dipyridamole (Persantine®)	Tablets: 25 mg, 50 mg, 75 mg	150 - 400 mg/day	400 mg per day
Dipyridamole Extended Release/Aspirin (Aggrenox®)	Capsule: 200 mg dipyridamole/25 mg aspirin	1 cap bid	1 cap bid
Ticlopidine (Ticlid®)	Tablets: 250 mg	250 mg bid	250 mg bid; higher doses do not result in further platelet impairment.

1 **Indication for use**

Antiplatelet agents are used for a variety of cerebrovascular and cardiovascular disorders including prevention of myocardial infarction and use in cardiovascular stenting. This review will address the use of these agents in managing stroke.

Table 3. Antiplatelet agents- Indications for Use[16,17,20,22,24]

Agent	FDA-labeled indication	Unlabeled Uses
Aspirin	Fever; conditions requiring chronic aspirin therapy for pain and/or inflammation; reduce the risk of death and/or nonfatal MI in patients with a previous MI or unstable angina pectoris; to reduce the risk of vascular mortality in patients with a suspected acute MI; primary prevention of an MI	Reduce recurrence of TIAs and risk of stroke and death; reduce risk of thrombosis and/or reocclusion of prosthetic or saphenous vein femoral popliteal bypass grafts; maintain patency following coronary or peripheral vascular angioplasty; treat peripheral vascular insufficiency caused by arteriosclerosis; treat Kawasaki disease.
Clopidogrel	Secondary prevention of myocardial infarction, stroke, and other vascular events	In combination with aspirin to prevent subacute thrombosis after coronary stent placement.
Dipyridamole	Adjunctive therapy to warfarin in the prevention of postoperative thromboembolic complications cardiac valve replacement.	Dipyridamole has been used in combination with aspirin and or anticoagulants to: treat lower extremity occlusive vascular disease; prevent recurrent TIAs or MI and reduce the risk of stroke and death; prevent thromboembolism following PTCA; prevent stroke following coronary stent insertion; maintain artery bypass grafts.
Dipyridamole/aspirin	Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	Treat lower extremity occlusive vascular disease; prevent recurrent TIAs or MI and reduce the risk of stroke and death; prevent thromboembolism following PTCA; prevent stroke following coronary stent insertion; maintain artery bypass grafts.
Ticlopidine	Secondary prevention of thrombotic stroke for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy	Stroke prevention following coronary stent insertion in conjunction with aspirin and/or dipyridamole

1. Duration of therapy

Most patients will require indefinite treatment.

2. Duplicative therapy

Duplicative therapy is not indicated unless the patient has a subsequent stroke on the preventative antiplatelet agent. If the patient does develop a stroke, then most clinicians empirically either increase the aspirin dose or add a secondary agent (e.g., dipyridamole) or change to another agent (e.g., clopidogrel); however, this is not evidence based.

3. Drug-drug interactions

The following list describes clinically significant drug-drug interactions with the antiplatelet agents.[24-28]

a. **Antacids -** Antacids increase urinary pH and reduce the renal reabsorption of **aspirin** thus increasing clearance and decreasing the pharmacological effects. The magnitude of the antacid interaction depends

on the agent, dose and pretreatment urinary pH. Giving **ticlopidine** after antacids has resulted in an 18% decrease in ticlopidine plasma levels. Ticlopidine should be taken 1-2 hours before antacid dose. **Antacids, H2-receptor blockers, proton pump inhibitors** raise the gastric pH significantly and reduce the bioavailability of **dipyridamole**.

b. **Urinary alkalinizers** (e.g., sodium bicarbonate) may decrease the pharmacological effects of salicylates. The magnitude of the antacid interaction depends on the agent, dose and pretreatment urinary pH. Antacids and urinary alkalinizers increase urinary pH and reduce the renal reabsorption of salicylate thus increasing salicylate clearance.

c. **Carbonic anhydrase inhibitors-** When oral **acetazolomide or diclofenamide** were given in combination with high dose **aspirin** (3.9 gm) salicylate intoxication occurred. Also, carbonic anhydrase inhibitors accumulate and may result in CNS depression and metabolic acidosis.

d. **Corticosteroids- Betamethasone, dexamethasone, prednisone, prednisolone, methylprednisolone and hydrocortisone** may increase risk of GI ulceration and increase salicylate clearance and decrease serum effectiveness; tailor salicylate dosage as needed. Monitor for salicylate toxicity if taking large doses of aspirin and tapering corticosteroid dosage down.

e. **Oral Anticoagulants- Warfarin** and **aspirin** may have additive hypoprothrombinemic effect and since aspirin impairs platelet function there is potential increased risk of bleeding. **Ticlopidine** inhibits R-warfarin metabolism and platelet aggregation with potential increased risk of bleeding; monitor INR regularly. **Clopidogrel** prolongs bleeding time and at high concentrations, clopidogrel may inhibit CYP2C9 and decrease the metabolism of warfarin. Concomitant administration of **dipyridamole** and **warfarin** does not appear to increase the frequency or severity of bleeding compared to warfarin alone.

f. **Heparin- Aspirin** can increase risk of bleeding in heparin anticoagulated patients. The safety of heparin and **clopidogrel** has not been established, monitor patients closely. **Danaparoid and low molecular weight heparin** like **enoxaparin** given with **dipyridamole** may result in increased risk of bleeding and increase risk of hematoma when neuroaxial anesthesia is employed.

g. **NSAIDs-** The combination of **NSAIDs with aspirin, clopidogrel, ticlopidine and dypyridamole/aspirin** may result in increased incidence of bleeding. The combination of **indomethacin and dipyridamole** may result in significantly reduced urine volume, sodium excretion, and renal filtration fraction leading to marked fluid retention. Monitor renal function especially in patients with cardiac or vascular problems.

h. **Aspirin-** The combination of **ticlopidine** and **aspirin** or **clopidogrel** and **aspirin** may result in increased bleeding; monitor patients for signs and symptoms of bleeding.

i. **Antihypertensive agents-** Effectiveness of **beta-blockers (e.g., propranolol, pindolol, labetalol), and ACE inhibitors (mainly enalapril),** may be reduced when given in combination with aspirin; monitor blood pressure. **Verapamil** 240 mg daily and **aspirin** 325 mg daily has resulted in abnormal bruising and prolonged bleeding times. This combination does not need to be normally avoided unless the patient becomes symptomatic.

j. **Methotrexate-** the combination of aspirin (975 mg) and methotrexate (10 mg) may result in increased methotrexate drug levels causing toxicity by interfering with protein binding and renal elimination of the antimetabolite

k. **Probenecid and sulfinpyrazone-** Salicylates in doses greater than 700 mg antagonize the uricosuric effect of probenecid and sulfinpyrazone.

l. **Sulfonylureas and Insulin-** Salicylates in doses > 2 gm/d have a hypoglycemic action. They may potentiate the glucose lowering effect of sulfonylureas and insulin.

m. **Cyclosporine-** The combination of cyclosporine and ticlopidine may result in a reduction of cyclosporine level second to increased metabolism; monitor levels.

n. **Eptifibatide, Reteplase, Streptokinase**- Administration of ticlopidine, clopidogrel, dipyridamole with either eptifibatide, reteplase, or streptokinase may result in increased risk of bleeding.

o. **Antiepileptics-** The administration of **ticlopidine** and **phenytoin or fosphenytoin** may result in elevated phenytoin levels and possible toxicity; monitor serum levels and adjust dose. **Ticlopidine** may inhibit **carbamazepine** metabolism; monitor carbamazepine plasma levels. **Aspirin** displaces **valproic acid** from its protein binding sites and may decrease its total body clearance; monitor for symptoms of valproic acid toxicity and/or serum levels.

p. **Theophylline -** The combination of **ticlopidine** and **theophylline** may result in elevated serum theophylline levels; monitor levels. The administration of **caffeine** or **theophylline** with **dipyridamole** may negate the coronary vasodilation caused by dipyridamole and interfere with dipyridamole thallium scintigraphy tests.

q. **Agents metabolized by P450 2C9**- At high concentrations in vitro, clopidogrel inhibits p450 2C9. **Clopidogrel** may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, torsemide** , and **fluvastatin** but there are no data to predict the magnitude of the interactions.

r. **Edrophonium, Distigmine bromide- Dipyridamole** may decrease the effectiveness of **edrophonium or distigmine bromide** and aggravate muscle weakness

s. **Adenosine -** The combination of **adenosine and dipyridamole** may result in adenosine toxicity secondary to decreased metabolism; a smaller dose of adenosine may be required.

Aspirin [24-28]

Criteria		Rationale
Usual dose range per day	50 –325 mg/day	Current FDA recommended dose for stroke prevention. Efficacy for stroke prevention has been shown with doses ranging from 50 mg/day to 1300 mg/day.
Indication for use	**Labeled:** Fever; conditions requiring chronic aspirin therapy for pain and/or inflammation; reduce the risk of death and/or nonfatal MI in patients with a previous MI or unstable angina pectoris; reduce the risk of vascular mortality in patients with suspected acute MI; primary prevention of an MI **Unlabeled:** Reduce recurrence of TIAs and the risk of stroke and death; reduce risk of thrombosis and/or reocclusion of prosthetic or saphenous vein femoral popliteal bypass grafts; maintain patency following coronary or peripheral vascular angioplasty; treat peripheral vascular insufficiency secondary to arteriosclerosis ; treat Kawasaki disease, pericarditis, rheumatic fever or antiphospholipid syndrome in pregnancy.	Supported by product labeling and clinical practice.
Duration of therapy	Most patients require indefinite therapy; however, must be individualized.	Patients who respond to therapy and do not have significant adverse effects should continue therapy.
Duplicity of therapy	Duplicative therapy is not indicated.	Patients who fail monotherapy could be tried on an alternative agent.

Drug-drug interactions

Alcohol	Increased risk of GI ulceration; ingestion of alcohol may also prolong bleeding time
Antacids Urinary alkalinizers (e.g., sodium bicarbonate)	May decrease the pharmacologic effects of salicylates. The magnitude of the antacid interaction depends on the agent, dose and pretreatment urinary pH. Antacids and urinary alkalinizers increase urinary pH and reduce the renal reabsorption of salicylate thus increasing salicylate clearance.
Carbonic anhydrase inhibitors	Salicylate intoxication has occurred after coadministration of high dose aspirin (3.9 gm) and oral acetazolamide or diclofenamide. Also, carbonic anhydrase inhibitors accumulate and may result in CNS depression and metabolic acidosis.
Corticosteroids	Corticosteroids increase salicylate clearance and decrease serum effectiveness; tailor salicylate dosage as needed. Monitor for salicylate toxicity if taking large doses of aspirin and tapering corticosteroid dosage down.
Oral Anticoagulants	Additive hypoprothrombinemic effect. Impaired platelet function. Use caution.
Heparin	Aspirin can increase risk of bleeding in heparin anticoagulated patients
NSAIDs	Increased incidence of GI side effects
Valproic Acid	Aspirin displaces valproic acid from its protein binding sites and may decrease its total body clearance; monitor for symptoms of valproic acid toxicity and/or serum levels.
Antihypertensive agents	Effectiveness of **beta-blockers (e.g., propranolol, pindolol, labetalol), and ACE inhibitors (mainly enalapril),** may be reduced when given in combination with aspirin; monitor blood pressure. **Verapamil** 240 mg daily and **aspirin** 325 mg daily has resulted in abnormal bruising and prolonged bleeding times. This combination does not need to be normally avoided unless the patient becomes symptomatic.
Methotrexate	Increased methotrexate drug levels causing toxicity by interfering with protein binding and renal elimination of the antimetabolite
Probenecid Sulfinpyrazone	Salicylates antagonize the uricosuric effect
Spironolactone	Salicylates may inhibit the diuretic effects; however antihypertensive action does not appear to be altered.
Sulfonylureas Insulin	Salicylates in doses > 2 gm/d have a hypoglycemic action. They may potentiate the glucose lowering effect of these drugs

Drug-disease interactions

Bleeding peptic ulcer	Exacerbate bleeding

Intracranial hemorrhage	Exacerbate bleeding
Severe hepatic impairment	May be at risk for bleeding diathesis.
G-6-PD or pyruvate kinase deficiency	Avoid in these patients, may aggravate hemolysis
Hypoprothrombinemia, vitamin K deficiency, von Willebrand's disease, hemophilia, thrombotic thrombocytopenic purpura	Increased risk of bleeding

Ticlopidine (Ticlid®) [17, 25-28]

Criteria		Rationale
Usual dose range per day	250 mg bid	Safety and efficacy of doses greater than 500 mg per day have not been studied.
Indication for use	**Labeled:** Adjunctive therapy to warfarin in the prevention of postoperative thromboembolic complications associated with the placement of mechanical prosthetic heart valves. **Unlabeled:** Stroke prevention following coronary stent insertion in conjunction with aspirin and/or dipyridamole	Supported by product labeling and clinical practice.
Duration of therapy	Most patients require indefinite therapy; however, must be individualized.	Patients who respond to therapy and do not have significant adverse effects should continue therapy
Duplicity of therapy	Duplicative therapy is not indicated.	Patients who fail monotherapy could be tried on an alternative agent.

Ticlopidine Drug Interactions

Antacids	Giving ticlopidine after antacids has resulted in an 18% decrease in ticlopidine plasma levels. Ticlopidine should be taken 1-2 hours before antacid dose.
Aspirin	Ticlopidine potentiates the effect of aspirin on collagen induced platelet aggregation; close monitoring of blood counts is warranted
Carbamazepine	Possible inhibition of carbamazepine metabolism; monitor carbamazepine plasma levels.
Cyclosporine	Reduction of cyclosporine level second to increased metabolism; monitor levels.
Eptifibatide/ reteplase/ streptokinase	Increased risk of bleeding.
NSAIDs	The combination of NSAIDs and ticlopidine may result in an increased incidence of bleeding.
Phenytoin/ Fosphenytoin	Elevated phenytoin levels and possible toxicity; monitor serum levels and adjust dose.
Theophylline	Elevated serum theophylline levels; monitor levels.
Warfarin	Inhibition of R-warfarin metabolism and inhibition of platelet aggregation with potential increased risk of bleeding; monitor INR regularly.
Disease-Drug Interactions	
Peptic Ulcer Disease	Ticlopidine prolongs bleeding time and increases risk of gastrointestinal bleeding.
Elective surgery	Ticlopidine should be discontinued 10-14 days prior to surgery.
Severe hepatic impairment	May be at risk for bleeding diathesis.
Intracranial hemorrhage	Exacerbate bleeding.

Clopidogrel (Plavix®) [16, 24-28]

Criteria		Rationale
Usual dose range per day	75 mg per day	Studied and accepted dose.
Indication for use	**Labeled:** Secondary prevention of myocardial infarction, stroke, and other vascular events **Unlabeled:** In combination with aspirin to prevent subacute thrombosis after coronary stent placement.	Supported by product labeling and clinical practice.
Duration of therapy	Most patients require indefinite therapy; however, must be individualized.	Patients who respond to therapy and do not have significant adverse effects should continue therapy.
Duplicity of therapy	Duplicative therapy is not indicated.	Patients who fail monotherapy could be tried on an alternative agent.

Clopidogrel Drug Interactions

Aspirin	Potential for increased bleeding; monitor patients for signs and symptoms of bleeding
Eptifibatide/ reteplase/ streptokinase	Increased risk of bleeding
Heparin	Safety of the combination not established; monitor patients closely
NSAIDs	Increased occult gastrointestinal blood loss.
Warfarin	Clopidogrel prolongs bleeding time; increased risk of bleeding. At high concentrations, clopidogrel may inhibit CYP2C9 and decrease the metabolism of warfarin.
Phenytoin, tamoxifen, tolbutamide, torsemide fluvastatin	At high concentrations in vitro, clopidogrel inhibits p450 2C9. Clopidogrel may interfere with the metabolism of these drugs but there are no data to predict the magnitude of the interactions.
Disease-Drug Interactions	
Bleeding peptic ulcer	Exacerbate bleeding
Intracranial hemorrhage	Exacerbate bleeding
Severe hepatic impairment	May be at risk for bleeding diathesis.
Elective surgery	Clopidogrel should be discontinued 7 days prior to surgery.

Dipyridamole (Persantine®) [20,24-28]

Criteria		Rationale
Usual dose range per day	75-100 mg QID	Studied and accepted dose.
Indication for use	**Labeled:** Adjunctive therapy to warfarin in the prevention of postoperative thromboembolic complications associated with the placement of mechanical prosthetic heart valves. **Unlabeled:** Stroke prevention following coronary stent insertion; use in conjunction with aspirin to treat lower extremity occlusive vascular disease; prevent recurrent TIAs and reduce the risk of stroke and death; secondary prevention of myocardial infarction; prevent thromboembolism following PTCA, in conjunction with aspirin.	Supported by product labeling and clinical practice.
Duration of therapy	Most patients require indefinite therapy; however, must be individualized.	Patients who respond to therapy and do not have significant adverse effects should continue therapy.
Duplicity of therapy	Duplicative therapy is not indicated.	Patients who fail monotherapy could be tried on an alternative agent.

Dipyridamole Drug Interactions

Antacids H2-receptor blockers Proton pump inhibitors	Drugs which raise the gastric pH significantly are expected to reduce the bioavailability of dipyridamole
Caffeine Theophylline	May negate the coronary vasodilation caused by dipyridamole and interfere with dipyridamole thallium scintigraphy tests
Indomethacin	The combination significantly reduced urine volume, sodium excretion, and renal filtration fraction and may result in marked fluid retention. Monitor renal function especially in patients with cardiac or vascular problems.
Anticoagulants	Concomitant administration of dipyridamole and warfarin does not appear to increase the frequency or severity of bleeding compared to warfarin alone; monitor for potential bleeding.
Edrophonium Distigmine bromide	Decreased effectiveness; aggravate muscle weakness
Adenosine	Adenosine toxicity secondary to decreased metabolism; a smaller dose of adenosine may be required
Danaparoid Low molecular weight heparins	Increased risk of bleeding and increase risk of hematoma when neuroaxial anesthesia is employed
Eptifibatide Reteplase Streptokinase	Increased risk of bleeding
Disease-drug interactions	
Myasthenia gravis	May unmask myasthenia gravis or may increase muscle weakness
Hypotension	May worsen hypotension as dipyridamole can cause peripheral vasodilation.

Dipyridamole Extended Release/Aspirin [15,25-29]

Criteria		Rationale
Usual dose range per day	25/200 mg (1 cap) BID	Studied and accepted dose.
Indication for use	**Labeled:** Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis. **Unlabeled:** Treat lower extremity occlusive vascular disease; prevent recurrent TIAs or MI and reduce the risk of stroke and death; prevent thromboembolism following PTCA; prevent stroke following coronary stent insertion; maintain artery bypass grafts.	Supported by product labeling and clinical practice.
Duration of therapy	Most patients require indefinite therapy; however, must be individualized.	Patients who respond to therapy and do not have significant adverse effects should continue therapy.
Duplicity of therapy	Duplicative therapy is not indicated.	Patients who fail monotherapy could be tried on an alternative agent.

Drug-drug interactions

Alcohol	Increased risk of GI ulceration; ingestion of alcohol may also prolong bleeding time
Antacids Urinary alkalinizers	May decrease the pharmacologic effects of salicylates. The magnitude of the antacid interaction depends on the agent, dose and pretreatment urinary pH.
Carbonic anhydrase inhibitors	Salicylate intoxication has occurred after coadministration of high dose aspirin (3.9 gm) and oral acetazolamide or diclofenamide. Also, carbonic anhydrase inhibitors accumulate and may result in CNS depression and metabolic acidosis.
Corticosteroids	Corticosteroids increase salicylate clearance and decrease serum levels
Oral Anticoagulants	Aspirin and warfarin have an additive hypoprothrombinemic effect and aspirin impairs platelet function. Use caution. Concomitant administration of dipyridamole and warfarin does not appear to increase the frequency or severity of bleeding compared to warfarin alone; monitor for potential bleeding.
Heparin/ Danaparoid/ Low mol. weight heparin	Aspirin can increase risk of bleeding in heparin anticoagulated patients. Dipyridamole increases the risk of bleeding and increases risk of hematoma when neuroaxial anesthesia is employed
NSAIDs	Increased incidence of GI side effects
Valproic Acid	Aspirin displaces valproic acid from its protein binding sites and may decrease its total body clearance
Methotrexate	Increased methotrexate drug levels causing toxicity by interfering with protein binding and renal elimination of the antimetabolite
Probenecid Sulfinpyrazone	Salicylates antagonize the uricosuric effect
Antacids H2-receptor blockers Proton pump inhibitors	Drugs which raise the gastric pH significantly are expected to reduce the bioavailability of dipyridamole
Caffeine Theophylline	May negate the coronary vasodilation caused by dipyridamole and interfere with dipyridamole thallium scintigraphy tests
Edrophonium Distigmine bromide	Decreased effectiveness; aggravate muscle weakness
Adenosine	Adenosine toxicity secondary to decreased metabolism; a smaller dose of adenosine may be required
Eptifibatide Reteplase Streptokinase	Increased risk of bleeding

Disease-drug interactions	
Myasthenia gravis	May unmask myasthenia gravis or may increase muscle weakness
Hypotension	May worsen hypotension as dipyridamole can cause peripheral vasodilation.
Bleeding peptic ulcer	Exacerbate bleeding
Intracranial hemorrhage	Exacerbate bleeding

Severe hepatic impairment	May be at risk for bleeding diathesis.
G-6-PD or pyruvate kinase deficiency	Avoid in these patients, may aggravate hemolysis
Hypoprothrombinemia, vitamin K deficiency, von Willebrand's disease, hemophilia, thrombotic thrombocytopenic purpura	Increased risk of bleeding

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Drug List Appendix

Sulfonylureas
Acetohexamide (Dymelor®)
Chlorpropamide (Diabinese®)
Glimepiride (Amaryl®)
Glipizide (Glucotrol®)
Glyburide (DiaBeta®, Micronase®)
Tolazamide (Tolinase®)
Tolbutamide (Orinase®)

Carbonic Anhydrase Inhibitors
Acetazolamide (Diamox®)
Dichlorphenamide (Daranide®)
Methazolamide (Neptazane®)

Urinary alkalinizers
Potassium citrate (Urocit-K®, K-lyte®)
Sodium acetate
Sodium bicarbonate
Sodium citrate (Bicitra®, Oracit®)
Sodium lactate
Tromethamine (Tham®)

Antacids
Aluminum hydroxide
Aluminum magnesium hydroxide
Magnesium hydroxide

H2-receptor antagonists
Cimetidine (Tagamet®)
Ranitidine (Zantac®)
Famotidine (Pepcid®)
Nizatidine (Axid®)

Proton Pump Inhibitors
Omeprazole (Prilosec®)
Lansoprazole (Prevacid®)
Rabeprazole (Aciphex®)
Pantoprazole (Protonix®)

Corticosteroids
Betamethasone (Celestone®)
Dexamethasone (Decadron®)
Hydrocortisone (Cortisone®)
Prednisone (Deltasone®)
Prednisolone (Prelone®)
Methylprednisolone.(Medrol®)

Anticoagulants
Warfarin (Coumadin®)
Anisindione (Miradon®)
Dicumarol (Dicumarol®)
Eptifibatide
Alteplase (Activase®)
Reteplase (Retavase)
Streptokinase (Kabikinase®)
Heparin
Danaparoid (Orgaran®)
Enoxaparin (Lovenox®)
Dalteparin (Fragmin®)
Ardeparin (Normiflo®)

Nonsteroidal antiinflammatory agents
Indomethacin (Indocin®)
Ibuprofen (Advil®, Motrin®)
Naproxen (Naprosyn®, Naprelan®)
Naproxen sodium (Anaprox®, Aleve®)
Flurbiprofen (Ansaid®)
Ketoprofen (Orudis®)
Ketorolac (Toradol®)
Diflunisal (Dolobid®)
Fenoprofen (Nalfon®)
Oxaprozin (Daypro®)
Diclofenac (Voltaren®)
Etodolac (Lodine®)
Nabumetone (Relafen®)
Sulindac (Clinoril®)
Tolmentin (Tolectin®)
Piroxicam (Feldene®)
Meclofenamate (Meclomen®)
Celecoxib (Celebrex®)
Rofecoxib (Vioxx®)

Beta-blockers
Acebutolol HCl (Sectral?)
Atenolol (Tenormin?)
Betaxolol (Kerlone?)
Bisoprolol (Zebeta?)
Carteolol (Cartrol?)
Carvedilol (Coreg?)
Labetalol (Trandate?)
Metoprolol (Lopressor?)
Nadolol (Corgard?)
Penbutolol (Levatol?)
Pindolol (Visken?)
Propranolol (Inderal?)
Sotalol HCl (Betapace?)
Timolol (Blocadren?)

Immunosuppressants
Methotrexate (Methotrexate®)
Cyclosporine (Neoral®, Sandimmune®)

ACE inhibitors
Lisinopril (Prinivil®, Zestril®)
Benazepril (Lotensin®)
Fosinopril (Monopril®)
Ramipril (Altace®)
Quinapril (Accupril®)
Trandolapril (Mavik®)
Captopril (Capoten®)
Enalapril (Vasotec®)
Moexipril (Univasc®)

Antiepileptics
Phenytoin (Dilantin®)
Fosphenytoin (Cerebyx®)
Carbamazepine (Tegretol®)
Valproic acid (Depakote®, Depakene®)

BENZODIAZEPINE AGONIST AGENTS

MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

The benzodiazepines possess at least five properties that make them useful in a variety of disorders: amnesic, anxiolytic, anticonvulsant, muscle relaxant and sedative. The benzodiazepines offer several advantages over other central nervous system depressant drugs including a relatively low incidence of adverse effects, decreased acute toxicity, lower abuse potential and fewer drug interactions.[1-4]

Zaleplon and zolpidem are sedative and hypnotic agents structurally unrelated to the benzodiazepines and other sedative and hypnotic agents. Zaleplon interacts with the GABA-benzodiazepine receptor complex and produces sedative, anxiolytic, anticonvulsive and muscle relaxant effects similar to the benzodiazepines in animal models.[5] Zolpidem does not possess the amnesic, anxiolytic, anticonvulsant or muscle relaxant properties of the benzodiazepines at hypnotic doses.[6,7]

The mechanism of action of the benzodiazepines is enhancement of the inhibitory effects of GABA. Three subtypes of benzodiazepine receptors have been identified. Currently available benzodiazepines do not preferentially bind to a specific receptor subtype with the exception of quazepam. Quazepam and one of its active metabolites, 2-oxyquazepam bind selectively to omega-1benzodiazepine receptors (BDZ-1). Quazepam's other major active metabolite desalkyloxo- quazepam, like other benzodiazepines, does not preferentially bind to a specific receptor subtype and may negate the selective binding of quazepam, especially with chronic use. The clinical significance of this selective binding is not known.[4,8] Pharmacological actions of the benzodiazepines are similar. The primary differences among the benzodiazepines are in their pharmacokinetic properties and these are often the main factors affecting drug selection.[1,2,4] See Table 1.

Zaleplon interacts with the GABA-benzodiazepine receptor complex producing anxiolytic, anticonvulsant, and sedative effects similar to the benzodiazepines in animal studies. Zaleplon and zolpidem preferentially bind to omega-1 benzodiazepine receptors (BDZ-1). The clinical significance of this selective binding is not known. The selectivity for omega-1 benzodiazepine receptors (BDZ-1) is not absolute.[5,7] Zaleplon has less potent amnesic effects than the benzodiazepines.[5,9] Zolpidem possesses minimal anxiolytic, amnesic, anticonvulsant or muscle relaxant properties at sedative doses.[6] In low doses, zaleplon and zolpidem do not significantly alter sleep stages or time in REM sleep compared with the benzodiazepines which increase time in Stages I and II and decrease time in Stages III and IV and REM sleep. Whether this has an impact on clinical effects of these drugs, has not been determined.[5,6,7,9] The relatively fast onset and short half-lives of these two agents make them suitable for the suitable for the short-term treatment of insomnia. See Table 1.

1. **Maximum usual dosage**: Table 2 contains usual dosage ranges and maximum recommended doses for the benzodiazepine agonists. Approximate equivalent doses are presented when available. Doses are those recommended in adults unless otherwise indicated. There is a high degree of interpatient variability in response to the benzodiazepine agonists. The recommended dosage ranges are broad guidelines. In most cases, therapy should be started with the lowest dose and titrated upward until the desired response is achieved. In the treatment of alcohol withdrawal, larger doses are used initially to control symptoms and then tapered as tolerated.[1,2,4,8]

   a. **Dosing in the Elderly.** The capacity for oxidative metabolism decreases with age. The volume of distribution of lipid soluble drugs increases with age. Both effects lead to reduced clearance

of benzodiazepine agonists and active metabolites in elderly patients.[1,8] Two of the three benzodiazepines eliminated by conjugation rather than oxidation, lorazepam and oxazepam, do not have significantly longer half-lives in the elderly compared with younger patients.[1,4,10] The half-life of alprazolam, which is also eliminated by conjugation, was increased by approximately 30% in a group of healthy elderly subjects compared with younger adults.[8]

The pharmacokinetics of zaleplon were not significantly different in a group of elderly subjects compared with young, healthy subjects.[9] Zolpidem's half-life increased by approximately 30% in a group of patients aged 65 to 85, compared with younger patients.[6] Increased pharmacodynamic effects of the benzodiazepines are also seen in the elderly.[4] Recommended starting doses of benzodiazepine agonists for patients over the age of 65 are generally one-third to one-half of those for healthy, younger adults.[1,4,10] Specific dosage recommendations, where available are included in Table 2.

b. **Tolerance** to the sedative, muscle relaxant and anticonvulsant activities of benzodiazepines develops over time.[1,4] For treatment of seizure disorders, as many as 30% of patients on clonazepam or diazepam demonstrated a loss of efficacy, many within three months. In some cases, dosage adjustment may reestablish seizure control.[8] When used for more than two to four weeks, tolerance to sedative effects has been reported. For benzodiazepines with shorter half-lives, this can result in early morning wakening and increased daytime anxiety or nervousness.[8] The anxiolytic or antipanic efficacies do not appear to decrease over time, although use of benzodiazepines has not been evaluated in long-term trials (greater than four to six months).[1,8] Patients taking benzodiazepines for anxiety or panic disorder, without a history of substance abuse, were unlikely to require increasing doses of benzodiazepines.[2,11]

Reports of tolerance to the effects of zaleplon and zolpidem are mixed. Several reports found no significant development of tolerance with zolpidem when given up to twelve weeks. In the only comparison of zolpidem with a benzodiazepine, both triazolam and zolpidem had similar decreases in sleep versus wake time over the 28-day treatment period.[7]
Zaleplon has not been compared with benzodiazepines, nor has long term use been studied to determine the potential for development of tolerence.[9]

2. **Indication for use:** Benzodiazepines are the drugs of choice for a variety of indications in psychiatric illnesses and other medical disorders. These include treatment of anxiety and panic disorders, muscle spasms, seizures, agitation and insomnia. Their sedative, amnesic and anxiolytic effects also make the benzodiazepines first line agents for conscious sedation.[1-4] The labeled indications for the 14 benzodiazepines currently available in the United States are diverse. These variations in labeled indications generally represent differences in marketing decisions by the manufacturers rather than differences in pharmacological properties of the agents. Differences between the benzodiazepines are also based on their pharmacokinetic profiles. Onset, duration of action, available formulations, and elimination pathways determine suitability of an agent for a particular situation.[2,4]

Zaleplon has anxiolytic, anticonvulsant, and muscle relaxant properties similar to the benzodiazepines in animal models.[5] Information on zaleplon for these indications in humans has not been published.
Zolpidem has minimal anxiolytic, amnesic, anticonvulsant or muscle relaxant effects. Both drugs are indicated for the short-term treatment of insomnia.[6,7,12]

The most common indications for the benzodiazepine agonists are summarized below:

a. **Generalized anxiety disorder.** Benzodiazepines are the drug of choice in treating generalized anxiety disorder. In comparison with other anxiolytic agents such as antidepressants, ?-blockers, and neuroleptics, benzodiazepines have a faster onset and greater efficacy.[2,10,12]

b. **Panic disorder**. Alprazolam has been shown effective in the treatment of panic disorder with or without agoraphobia, with a faster onset than that of tricyclic antidepressants and selective serotonin reuptake inhibitors. Studies using other benzodiazepines such as diazepam, lorazepam, and oxazepam demonstrated anti-panic effects similar to alprazolam.[2,10,12]

c. **Sleep disorders.** Benzodiazepine agonists are the drugs of choice for the symptomatic relief of insomnia, because of their favorable side effect profile. Preferred agents for sleep disorders are those with a quick onset of action and short half-life, minimizing daytime sedation. Benzodiazepines also alleviate the sensory and motor symptoms characterizing restless leg syndrome, although development of tolerance to these effects can be a problem.[1,3,12]

d. **Status Epilepticus.** Because of their fast onset of action, benzodiazepines are generally considered the initial drugs of choice in the treatment of status epilepticus. Diazepam, lorazepam and midazolam are suited to treatment of status epilepticus. They can be given by IV push with an average onset of three to five minutes. Lorazepam is generally the preferred agent with its longer duration of action. Diazepam is available as a gel for rectal administration with a fast onset, providing more immediate treatment in the home setting.[1,4]

e. **Seizure disorders.** The benzodiazepines are indicated as adjunctive therapy in a variety of seizure disorders in patients not adequately controlled on other agents.[1,13]

f. **Muscle spasms.** Among their other pharmacological effects, the benzodiazepines are highly effective skeletal muscle relaxants. Diazepam is the most frequently used benzodiazepine for this indication. Diazepam provides an alternative to patients with inadequate response to baclofen.[1,10,13]

g. **Alcohol Withdrawal.** Symptoms of withdrawal in chronic users of alcohol can range from tremor and tachycardia to seizures, hypertension and hyperthermia. Severe alcohol withdrawal is life threatening. Because of their longer duration of action, benzodiazepines can be tapered more gradually, decreasing the potential for the more serious effects of acute alcohol withdrawal including seizures. Transference of dependence to the benzodiazepine is highly probable. Rapid tapering of the benzodiazepine, with close monitoring and follow-up is recommended.[4]

Table 1. Benzodiazepines-pharmacokinetic properties[1,4-6,8,10]

Drug	Onset after oral administration	Protein Binding	Elimination half-life (hours)	Active metabolites*	Major pathway of metabolism
Alprazolam	Intermediate	80%	12 to 15	Insignificant	Oxidation
Chlordiazepoxide	Intermediate	90 to 98%	5 to 30	Desmethylchlordiaze-poxide Demoxepam	Oxidation
Clonazepam	Fast	85%	18 to 50	Insignificant	Oxidation
Clorazepate Dipotassium	Intermediate	80 to 95%	Not significant	Desmethyldiazepam	Oxidation
Diazepam	Very fast	98%	20 to 80	Desmethyldiazepam	Oxidation
Estazolam	Intermediate	93%	10 to 30	Insignificant	Oxidation
Flurazepam Hydrochloride	Fast	97%	40 to 114	Desalkylflurazepam	Oxidation
Halazepam	Slow		Not significant	Desmethyldiazepam	Oxidation
Lorazepam	Intermediate	85 to 92%	10 to 20	None	Conjugation
Midazolam	Very Fast	95 to 99%	2 to 5	None	Oxidation
Oxazepam	Slow	86 to 96%	5 to 20	None	Conjugation
Quazepam	Fast	95 to 99%	25 to 40	2-oxoquazepam, desalkyloxoquazepam	Oxidation
Temazepam	Intermediate	96%	10 to 20	Insignificant	Conjugation
Triazolam	Intermediate	89 to 94%	1.5 to 5	Insignificant	Oxidation
Zaleplon	Very Fast	60%	1	None	Oxidation
Zolpidem	Fast	92%	2.5	None	Oxidation Hydroxylation

? The active metabolite desmethyldiazepam has a half-life in adults of 60 to 120 hours, demoxepam 14 to 119 hours, desalkylflurazepam 47 to 100 hours, quazepam's metabolites 40 to 110 hours. This can extend the effects of a benzodiazepine with a relatively short half-life and account for cumulative adverse effects.

Table 2. Benzodiazepine agonists - usual and maximum dosage[1,6,8,9,12-15]

Drug	Dosage Form(s)	Approximate Equivalent Dose	Usual Starting Dose	Usual Maintenance Dose	Maximum Daily Dose
Alprazolam (Xanax®)	**Tablets**: 0.25mg, 0.5mg, 1mg, 2mg **Oral Concentrate:** 1mg/ml (30mL) **Oral Solution:** 0.5 mg/5mL (500 mL)	0.5 mg	0.25 to 0.5 mg tid **Elderly patients:** 0.125 to 0.25 mg po bid	0.5 to 4 mg per day. Higher doses may be needed for treatment of panic disorder.	10 mg
Chlordiaze-poxide (Librium®)	**Capsules:** 5mg, 10mg, 25mg **Tablets:** 5mg, 25mg **Powder for injection:** 100mg/ vial	10 mg	**Oral:** 5 to 10 mg tid to qid **Elderly patients:** 5 to 10 mg bid **Injectable:** 50 to 100 mg	**Oral:** 5 to 25 mg tid to qid **Elderly oral:** 5 to 10 mg bid to qid **Alcohol withdrawal:** 50 to 100 mg IM or IV (may repeat q 2-4 hours prn **Acute anxiety disorders:** 50 to 100 mg IM or IV, followed by 25 to 50 mg tid to qid **Pre-operative sedation:** 50 to 100 mg IM or IV	300 mg
Clonazepam (Klonopin®)	**Tablets:** 0.125mg, 0.25mg, 0.5mg, 1mg, 2mg	Not available	**Seizures:** 0.5 mg tid **Panic Disorder:** 0.25 mg bid **Infants:** 0.01 mg/kg/day given bid to tid **Children:** 0.03 mg/kg/day given bid to tid	**Adults:** 0.5 to 20 mg/day given bid to tid **Infants and Children:** 0.1 to 0.2 mg/kg/ day given bid to tid	**Seizures**: 20 mg **Panic Disorder:** 4 mg **Infants and Children:** 0.2 mg/kg
Clorazepate Dipotassium (Various)	**Tablets:** 3.75mg, 7.5mg, 15mg **†SD Tablets:** 11.25mg, 22.5mg	7.5 mg	7.5 mg tid **Alcohol withdrawal:** 30 mg tid, taper as tolerated **Children 9 to 12 years old:** 7.5 mg bid **Elderly:** 7.5mg bid	15 to 90 mg/day given bid to tid **Children 9 to 12 years old:** 15 to 60 mg/day given bid to tid	90 mg **Children 9 to 12 years old:** 60 mg

Drug	Dosage Form(s)	Approximate Equivalent Dose	Usual Starting Dose	Usual Maintenance Dose	Maximum Daily Dose
Diazepam (Valium®, Diastat®)	**Tablets:** 2mg, 5mg, 10mg **‡Capsules (sustained release):** 15mg **Oral Solution:** 1mg/mL (500mL) **Oral Concentrate:** 5mg/mL **Rectal Gel:** 5mg/mL in 0.5mL, 1mL, 2mL, 3mL, 4mL delivery syringes (2 doses per package) **Injectable solution:** 5mg/mL (1mL, 2mL, 10 mL) **¶Injectable suspension:** 5mg/mL	5 mg	**Tablets:** 2 mg bid to qid **Elderly patients:** 2 mg qd to bid **Alcohol withdrawal symptoms:** 10 mg qid **Children over 6 months:** 1 to 2.5 mg tid to qid **Injection:** 2 to 10 mg IM or IV	**Tablets:** 2 to 10 mg tid to qid **Capsules***** **Injection for acute anxiety:** 2 to 10 mg IM or IV repeated every 4 to 6 hours **Injection for status epilepticus:** 5 to 10 mg IV repeated every 10 to 15 minutes up to 30 mg. May repeat in 2 to 4 hours as necessary. Infants over 30 old: 0.2 to 0.5 mg every 2 to 5 minutes up to 5 mg IV. Children over 5 years old: 1 mg every 2 to 5 minutes up to10 mg. **Rectal gel:** mg/kg dose determined dependent upon the patient's age.	Maximum daily dose not defined **Rectal gel** should not be used for more than 5 episodes per month and for no more than 1 episode every 5 days.
Estazolam (Prosom®)	**Tablets:** 1mg, 2mg	1mg	1mg hs **Elderly patients:** 0.5 mg hs	1 to 2 mg po hs	2 mg
Flurazepam Hydro-chloride (Dalmane®)	**Capusles:** 15mg, 30mg	15mg	30 mg hs **Elderly patients:** 15 mg hs	30 mg hs **Elderly patients:** 15 to 30 mg hs	30 mg
Halezepam (Paxipam®)	**Tablets:** 20mg, 40mg	20 mg	20 mg tid to qid	80 to 160 mg per day given tid to qid	160 mg
Lorazepam (Ativan®)	**Tablets:** 0.5mg, 1mg, 2mg **Oral solution:** 2mg/mL **Solution for Injection:** 2mg/mL, 4mg/mL	1 mg	**Oral:** 2 to 3 mg bid to tid **Elderly patients:** 0.5 to 1 mg bid to tid	**Oral:** 1 to 10 mg/day given tid to qid or 2 to 4 mg hs **Injectable (pre-op):** 0.05 mg/kg IM or 0.044 mg/kg IV up to 2 mg **Injectable (status epilepticus):** 0.1 mg/kg (max 4 mg), may repeat in 15 minutes	10 mg

Drug	Dosage Form(s)	Approximate Equivalent Dose	Usual Starting Dose	Usual Maintenance Dose	Maximum Daily Dose
Midazolam (Versed®)	**Syrup:** 2mg/mL **Solution for Injection:** 1mg/mL, 5mg/mL	15 mg (oral)	**Oral as premedication:** 0.15 mg/kg up to 20 mg. **Injectable:** Titrated to effect Loading dose for rapid sedation: 0.01 to 0.05 mg/kg IV	Not applicable	**Oral:** 20 mg **Injectable:** none given
Oxazepam (Serax®)	**Tablets:** 15mg **Capsules:** 10mg, 15mg	15 mg	10 mg tid to qid **Elderly:** 10 mg tid **Alcohol withdrawal:** 15 to 30 mg qid	10 to 30 mg tid to qid **Elderly:** 10 to 15 mg tid to qid	120 mg
Quazepam (Doral®)	**Tablets:** 7.5mg, 15mg	15 mg	15 mg hs	7.5 to 15 mg hs	15 mg
Temazepam (Restoril®)	**Capsules:** 7.5mg, 15mg, 30mg	15 mg	15 to 30 mg hs **Elderly:** 15mg hs	15 to 30 mg hs **Elderly:** 7.5 to 30 mg hs	30 mg
Triazolam (Halcion®)	**Tablets:** 0.125mg, 0.25mg	0.25 mg	0.25 mg hs **Elderly:** 0.125 mg hs	0.125 to 0.5 mg hs	0.5 mg
Zaleplon (Sonata®)	Capsules: 5mg, 10mg.	NA	10 mg hs **Elderly:** 5 mg hs	5 to 20 mg hs **Elderly:** 5 to 10 mg hs	20 mg
Zolpidem (Ambien®)	Tablets: 5mg, 10mg.	15 mg	10 mg hs **Elderly:** 5 mg hs	5 to 10 mg hs **Elderly:** 5 to 10 mg hs	10 mg

†Patients stabilized on clorazepate T-TABS, may be switched to clorazepate SD tablets in the same daily dose given as a single dose every 24 hours.

‡Patients stabilized on doses of 15 mg or more per day may be converted to diazepam sustained release capsules in the same daily dose given every 24 hours.

¶Diazepam emulsion should be administered intravenously only.

3. Duration of therapy.

Benzodiazepines are used in a number of chronic illnesses, requiring long-term therapy. There are no standard guidelines for determining duration of therapy with benzodiazepines. Concerns of physiological dependence and abuse potential of the benzodiazepines have led to decreased use of these agents in the past few decades. Many of the conditions treated with benzodiazepines are characterized by subjective symptoms. Recent surveys indicate that attitudes about the conditions

being treated and overestimation of the risk for abuse of benzodiazepines have resulted in avoidance of benzodiazepines even in situations where strong evidence is available supporting their efficacy. Prescribers, in many cases, substituted less effective medications with higher potential for toxicity.[2,4] Animal studies used to measure abuse potential of zaleplon, indicated a dependence-producing profile equivalent to benzodiazepines and zolpidem.[5]

a. **Physical dependence** is characterized by physical withdrawal symptoms upon discontinuation. With the benzodiazepines, physical dependence can occur even at low therapeutic doses. The risk of physical dependence increases with dose, duration of treatment, severity of symptoms, use of benzodiazepines with a rapid onset, short duration of action and high potency.[1,2,4] In patients requiring long term therapy with benzodiazepines, use of a long acting benzodiazepine with a slow onset of action may decrease the risk of dependence and withdrawal.

b. **Withdrawal and rebound** symptoms may occur when benzodiazepines are discontinued. Symptoms of benzodiazepine withdrawal include anxiety, insomnia, tremor, tachycardia, sweating, light sensitivity, depersonalization, distraction, nightmares, hallucinations, and seizures. Withdrawal symptoms refer to those not present prior to benzodiazepine treatment. Rebound symptoms are recurrence of symptoms seen prior to benzodiazepine therapy. Intensity of rebound symptoms is higher than the intensity of original symptoms. The incidence and degree of withdrawal symptoms depend on the duration, dose and half-life of the benzodiazepine. Withdrawal symptoms are more likely with high doses for more than four to six weeks or lower doses for two to four months or longer.[1,4] Onset of withdrawal symptoms for short-acting benzodiazepines occurs within 24 to 48 hours, with peak severity at two to three days after discontinuation. For long-acting benzodiazepines, onset of withdrawal is slower occurring three to seven days after discontinuation.[1,2]

Due to the potential for withdrawal symptoms, it is recommended that benzodiazepines be tapered gradually. Several tapering regimens have been proposed. In general, it is recommended that the dose be tapered by one eighth to one fourth of the original dose every one to two weeks. Within this range, patients on higher doses, shorter acting benzodiazepines should be tapered more slowly. Withdrawal symptoms are more likely towards the end of the taper, so the last weeks of the taper should be more gradual.[1,2,4]

Rebound insomnia was seen with zaleplon during nights one and two after 28-day treatment with zaleplon. Rebound symptoms appeared to be dose related. Withdrawal, defined as three or more new symptoms following discontinuation of zaleplon, was not significantly different from placebo following 14 and 28 days of nightly use.[5,9] Zaleplon has not been directly compared with the benzodiazepines with regard to withdrawal and rebound effects. Animal studies of withdrawal symptoms following discontinuation of zolpidem are mixed. Studies in humans suggest that rebound insomnia occurs following discontinuation of triazolam, but not zolpidem following nightly use. These results have been questioned because the two studies did not use equivalent doses of triazolam and zolpidem. Incidence of physical dependence is dose related.[7]

4. Duplicative therapy.

The benzodiazepine agonists have similar pharmacological effects. Generally, use of two or more benzodiazepine agonists at the same time is not indicated. In rare situations, differences in pharmacokinetic parameters may make use of two agents for different situations in the same patient a reasonable therapeutic choice.

5. Drug-drug interactions

Routine study of drug interactions is a recent requirement in the drug approval process. Information about drug interactions occurring with benzodiazepines is limited to drug interactions expected from basic pharmacokinetics and pharmacology as well as case reports of specific interactions.

Many of the drug interactions seen with the benzodiazepines are due to increases and decreases in hepatic metabolism.[16,17] Benzodiazepine agonists can be divided into two categories based upon the major route of metabolism. Lorazepam, oxazepam and temazepam undergo hepatic glucuronidation. Alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, halazepam, quazepam, midazolam, triazolam, zaleplon, and zolpidem undergo hepatic oxidation via the CYP450 enzyme system. Chlordiazepoxide, diazepam, clorazepate, flurazepam, prazepam, halazepam and quazepam have active metabolites that are also metabolized by this system. Inhibitors, as expected, increase benzodiazepine concentrations and effects. CYP450 enzyme inducers decrease benzodiazepine concentrations and effects. Most are metabolized primarily by the CYP450 3A isoenzymes, but other subsets are involved to lesser degrees.[14] Those drugs with a high first pass metabolism are most affected be inducers and inhibitors of metabolism. Zaleplon is metabolized by aldehyde oxidase as well as the CYP450 enzyme system. CYP450 enzyme inducers and inhibitors are less likely to alter zaleplon elimination because of this major alternate metabolic pathway.[9,10] The degree of protein binding of the benzodiazepine agonists also influences pharmacokinetic interactions seen with the benzodiazepines. These many variables make accurate prediction of drug interaction outcomes difficult. Since routine testing for and reporting of drug interactions has not been required for the many years most of these agents have been on the market, information on drug interactions with the benzodiazepine agonists is inconsistent and incomplete.[4,13,15,16]

Summarized below is information currently available on significant drug interactions with the benzodiazepine agonists.[1,4,6,8-10,13-17]

a. Alcohol and CNS depressants. Alcohol and other central nervous system depressant drugs (**narcotics, barbiturates**) will increase the effects of benzodiazepine agonists (e.g. sedation, psychomotor depression). These effects appear to be additive, not synergistic.

b. Antacids. The rate, but not the extent of absorption of benzodiazepine agonists is decreased when taken at the same time as **magnesium and aluminum antacids.** When a fast onset of action is desired, as in sleep induction, antacids should be taken at least two hours before the benzodiazepine agonist.

c. Anticonvulsants. Interactions between the benzodiazepines and older anticonvulsant medications are unclear. Diazepam and lorazepam have been reported to decrease **phenytoin** concentrations. It is uncertain whether other benzodiazepines have the same effect on phenytoin.

Both phenytoin and **phenobarbital** are expected to increase the oxidative metabolism of the benzodiazepines. Triazolam and midazolam, both drugs having a large first pass metabolism, are the only agents where significant changes in serum concentrations were noted. **Valproic acid** or **divalproex** would be expected to inhibit oxidative metabolism of the benzodiazepines. The extent of the proposed interaction is unknown. All three of the older anticonvulsants would be expected to have additive CNS depressive effects. **Gabapentin** also causes dizziness and sedation, but does not appear to alter benzodiazepine metabolism.

d. Antidepressants. Several cases of hallucinations and delirium in patients taking zolpidem along with an antidepressant agent have been reported. Agents involved include bupropion, desipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone and venlafaxine. One group has proposed that these side effects are due to increased levels of zolpidem. Several factors were present in these patients, putting them at risk for increased free levels of zolpidem. All reports were in patients taking more than 5 mg per day zolpidem. A disproportionate number of the patients were female. Female patients have 40% serum concentrations of zolpidem than men taking the same dose of zolpidem.[18] Zolpidem is highly protein bound. With the exception of venlafaxine, the antidepressants involved are also highly protein bound and may increase free zolpidem levels. Zolpidem is metabolized by the CYP450 3A enzyme system. Several of the antidepressants are inhibitors of this enzyme system.[14,18]

e. Azole antifungal agents. Ketoconazole and **itraconazole** are potent inhibitors of CYP3A enzyme activity, while **fluconazole** shows moderate inhibition of enzyme activity. The effect of these agents on benzodiazepine levels is highly variable. The effect is dependent upon the degree of first pass metabolism by oxidation and other routes of elimination for each benzodiazepine. Ketoconazole and itraconazole are contraindicated in patients on alprazolam or triazolam. Significant increases 100% to 200% in midazolam serum concentrations were noted in patients on ketoconazole. Moderate increases in the effects of chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, halazepam, triazolam, and zolpidem may be seen in patients on azole antifungal agents.

f. Digoxin. There are several case reports of increased **digoxin** serum concentrations after starting diazepam. Increases reported were moderate (50 to 100%), with moderate to severe symptoms of toxicity. Alprazolam, zaleplon, and zolpidem had no effect on digoxin pharmacokinetic parameters in healthy volunteers. No information is available on the other benzodiazepines. Monitoring for symptoms of digoxin toxicity is recommended.

g. Fluvoxamine inhibits the oxidative hepatic metabolism of benzodiazepines. The plasma concentrations of alprazolam and of diazepam were increased by 75% to 150% in patients receiving fluvoxamine. Other benzodiazepines which undergo oxidative hepatic metabolism, clonazepam, chlordiazepoxide, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam, triazolam would be affected similarly. The serum concentrations of lorazepam, which is metabolized by conjugation, were not affected by administration of fluvoxamine.

h. Levodopa. Observations in several Parkinson's patients treated with levodopa suggest that benzodiazepines may impair the therapeutic effect of levodopa. The mechanism of this effect is unknown. Observe for worsening of symptoms of Parkinson's disease when benzodiazepines are used in patients on levodopa.

i. Macrolide antibiotics. Erythromycin is a potent inhibitor of CYP450 3A and moderate

increases of benzodiazepine concentrations have been reported with concurrent use. **Clarithromycin** is expected to have mild effects on benzodiazepine oxidative metabolism. **Azithromycin** does not appear to affect benzodiazepine metabolism or effects.

j. **Methylxanthines. Theophylline** and **caffeine** have been shown to reverse the sedative effects of benzodiazepines. This effect is thought to be due to an increased clearance of the benzodiazepines as well as direct antagonism of the benzodiazepines. Patients on theophylline may require higher doses of benzodiazepine agonists.

k. **Miscellaneous inhibitors of benzodiazepine oxidative metabolism.** Mild increases in the half lives of benzodiazepines metabolized by oxidation have been seen in patients on **cimetidine, disulfiram, diltiazem, fluoxetine, isoniazid, and verapamil.** Increases in serum concentrations of 30 to 50% have been reported, along with rare cases of significant toxicity. Monitoring for adverse effects is recommended.

l. **Nefazodone.** Nefazodone is a potent inhibitor of CYP450 3A enzyme activity. Effects on benzodiazepine serum concentrations variable. Alprazolam serum concentrations increased by approximately 100% with concurrent use. Triazolam serum concentrations increased by approximately 400%, leading to significant adverse effects with concurrent use. Lorazepam and oxazepam were not affected by nefazodone administration. Information on other benzodiazepines is not available. Based on pharmacokinetics, midazolam serum concentrations would be expected to increase with concurrent nefazodone administration.

m. **Non-nucleoside reverse transcriptase inhibitors (NNRTIs). Delavirdine** and **Effiravenz** caused significant increases in serum concentrations and toxic effects with alprazolam and triazolam. Use of these agents together is not recommended. Similar effects would be expected with oral midazolam. Other benzodiazepines undergoing oxidative metabolism would be expected to have mild increases in serum concentrations and toxic effects. Careful monitoring and lower doses of benzodiazepines undergoing oxidative metabolism are recommended.

n. **Oral estrogen/progesterone contraceptives.** Mild increases in the half-lives of benzodiazepines metabolized by oxidation in women on combination oral contraceptives (50% to 100%). Progestin alone does not appear to affect benzodiazepine concentrations. It is unknown if **estrogen** supplementation has the same effect on benzodiazepine metabolism, but similar effects would be expected. Observe for increased effects of the benzodiazepines.

o. **Probenecid.** Approximately doubled half-life of lorazepam in a small group of healthy volunteers. It is thought that temazepam and oxazepam, which are also metabolized by conjugation, may be similarly affected by coadministration with probenecid.

p. **Protease inhibitors.** The protease inhibitors are potent inhibitors of benzodiazepine metabolism. Significant increases in benzodiazepine toxic effects have been noted with some of the benzodiazepines. Midazolam or triazolam use is contraindicated in patients on **aprenavir, indinavir, nelfinavir, ritonavir,** or **saquinavir**. Patients on **ritonavir** should not take clorazepate, diazepam, estazolam, flurazepam or halazepam. Moderate increases in other benzodiazepines are expected when given with the protease inhibitors, with the exception of lorazepam, oxazepam and temazepam.

q. **Rifamycins. Rifampin** is a potent inducer of oxidative metabolism. Significant decreases in

maximum serum concentrations (88%) and AUC (95%) of triazolam have been noted with almost complete elimination of therapeutic effects. In patients taking rifampin, use of a benzodiazepine not metabolized by the CYP450 3A system (lorazepam, oxazepam, and temazepam) is recommended. Similar effects would be expected with **rifabutin.**

6. Drug disease interactions.

a. Glaucoma. Benzodiazepines have demonstrated anticholinergic action in animal studies. Any drug with anticholinergic activity has the propensity to exacerbate narrow angle glaucoma by causing dilation of the pupil. Dilation of the pupils increases blockage of outflow of aqueous humor leading to increased intraocular pressure in narrow angle glaucoma. This is why benzodiazepines carry the contraindication for use in patients with narrow angle glaucoma. In patients with open angle glaucoma, the significance of blockage of aqueous humor outflow by anticholinergic drugs is lessened. Patients, with open angle glaucoma controlled by medications can use benzodiazepines without experiencing damaging increases in intraocular pressure.[4,8,10]

Zaleplon and zolpidem have not been shown to possess anticholinergic effects. Neither agent carries a precaution for use in patients with glaucoma.[6,9]

b. Hypoalbuminemia. Most of the benzodiazepine agonists are highly protein bound. Patients with hypoalbuminemia have a higher concentration of unbound (active) drug. Increased effects of the benzodiazepines at lower doses can be expected in patients with conditions associated with hypoalbuminemia such as end stage renal disease, liver disease, cancer and malnutrition. Benzodiazepine agonists with decreased protein binding such as alprazolam, lorazepam, and zaleplon are preferred in these patients.[8,10,9,12]

c. Pregnancy. An early case-controlled study reported an association between cleft palate in infants born to mothers taking diazepam. The study did not control for underlying medical conditions in the mothers, such as epilepsy. At the time, diazepam was a drug commonly used to treat epilepsy. The incidence of cleft palate in infants born to mothers with epilepsy on anticonvulsant medication is 5-6%, higher than incidence in the general population. Other studies have not found an increased risk of fetal abnormalities in infants whose mothers were taking benzodiazepines during the gestational period.[1,9,10] Children born to mothers taking benzodiazepines throughout pregnancy are at risk of withdrawal symptoms after delivery. Neonatal flaccidity has also been reported. Because of these concerns, benzodiazepines should be discontinued when possible in patients who are pregnant.[10,14,16] When used as sedative-hypnotic agents, some consider the risks of using benzodiazepines as outweighing the potential benefit. Manufacturers of benzodiazepines used primarily as sedative-hypnotic agents (estazolam, quazepam, flurazepam, temazepam, and triazolam) have labeled them as contraindicated in pregnancy, although the risk with occasional use must be weighed against the benefit of these agents.[8,13]

The effects of zaleplon and zolpidem have not been studied in pregnant women. It is not known whether withdrawal symptoms are likely to occur. Zolpidem is a weak muscle relaxant, compared with benzodiazepines in adults. Risk of neonatal flaccidity may be less than with benzodiazepines. Animal studies indicate a lack of teratogenicity at doses several times therapeutic doses.[6,9]

Alprazolam (Xanax®)[1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	**Anxiety disorders:** 0.75 to 4 mg. **Panic disorder:** 1 to 10 mg.	Product labeling. Higher doses may be necessary in the treatment of panic disorder. Controlled clinical trials used doses up to 10 mg/day, with a mean daily dose of 5 to 6 mg/day.
Indication for use	**Labeled uses:** Management of anxiety disorders. Short-term therapy of the symptoms of anxiety. Anxiety related to depression. Panic disorder with or without agoraphobia. **Unlabeled uses**: social phobia, agoraphobia. Premenstrual syndrome.	Comparative studies with other anxiolytic substances, such as antidepressants, ?-blockers, and neuroleptics, have demonstrated the greater efficacy of benzodiazepines. A series of short-term (up to ten weeks), placebo-controlled trials found alprazolam superior to placebo in the treatment of panic disorder.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.

Drug-drug interactions	
Alcohol/CNS depressants	May see additive central nervous system depressant effects.
Antacids	Decreased rate, but not extent of benzodiazepine absorption.
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Ketoconazole causes increases in serum concentrations of alprazolam 13 to 14 fold. Use of alprazolam in patients on ketoconazole or itraconazole is contraindicated. Fluconazole increases alprazolam levels to a lesser, but significant extent, decreasing the dose of alprazolam should be considered.
Fluvoxamine	Increased serum concentrations by 75 to 150% reported. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Nefazodone	Increased benzodiazepine serum concentrations by approximately 100%.

NNRTIs	Alprazolam is not recommended in patients on delavirdine or effiravenz. Increases in serum concentrations and toxic reactions have been reported. Other NNRTIs do not affect alprazolam concentrations.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives.
Protease inhibitors	Increases in levels of benzodiazepines metabolized by oxidation. Alprazolam should not be used in patients on ritonavir. Choice of a benzodiazepine metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Chlordiazepoxide (Librium®) [1,4,8,10,13-16]

Criteria		**Rationale**
Usual dose range per day	45 to 300 mg	Supported by product labeling and clinical use.
Indication for use	Management of anxiety disorders or short-term treatment of the symptoms of anxiety. For the symptomatic treatment of acute alcohol withdrawal. Treatment of preoperative anxiety or apprehension.	Supported by product labeling and long term clinical use. There is some evidence that chlordiazepoxide's anxiolytic effects are inferior to those of other benzodiazepines. Chlordiazepoxide decreases the symptoms of alcohol withdrawal, but pharmacokinetic properties of other benzodiazepines may make them more suited for this indication.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	

Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.
Digoxin	Increased levels of digoxin reported with diazepam. Monitor for symptoms of digoxin toxicity.
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Nefazodone	May see increased serum concentrations and effects of the benzodiazepine.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives.
Protease inhibitors	Increases in levels of benzodiazepines metabolized by oxidation expected. Chlordiazepoxide should not be used in patients on ritonavir. Choice of an agent metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the cP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Clonazepam (Klonopin®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	Adults: 0.5 mg/day to 20mg/day in 2 to 3 divided doses. Pediatric patients: 0.01mg/kg/day to 0.2 mg/kg/day in 3 divided doses.	Effective dose highly variable. Supported by product labeling.
Indication for use	Treatment of panic disorder with or without agoraphobia. Used alone or as an adjunct for the treatment of Lennox-Gastaut Syndrome, akinetic, myoclonic or absence seizures.	Two double-blind, controlled trials in adult outpatients found clonazepam significantly more effective than placebo in decreasing the number of panic attacks and severity of symptom scores. Several small trials of clonazepam, demonstrated a reduction in seizure frequency.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.

Drug-drug interactions	
Alcohol/CNS depressants	May see additive central nervous system depressant effects.
Antacids	Decreased rate, but not extent of benzodiazepine absorption.
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.
Digoxin	Increased levels of digoxin seen with diazepam. Monitor for symptoms of toxicity.
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Nefazodone	Increased serum concentrations and effects of the benzodiazepines.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives was observed.

Protease inhibitors	Increases in levels of benzodiazepines metabolized by oxidation expected. Clonazepam should not be used in patients on ritonavir. Choice of an agent metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Clorazepate Dipotassium (Tranxene®) [1,4,8,10,13-16]

Criteria		**Rationale**
Usual dose range per day	7.5 to 90 mg per day in divided doses. Clorazepate SD tablets may be given as a single dose at bedtime.*	Supported by product labeling and clinical experience.
Indication for use	Management of anxiety disorders or short-term treatment of the symptoms of anxiety. For the symptomatic treatment of acute alcohol withdrawal. Adjunctive treatment of partial seizures.	Clorazepate has been shown to have anti-panic effects similar to alprazolam at adequate doses. Clorazepate showed a significant decrease in the symptoms of alcohol withdrawal as compared with placebo and similar results as compared with diazepam. In small trials, patients with inadequately controlled seizures on other anticonvulsant medications had a decrease in seizure activity with the addition of clorazepate.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		

Alcohol/CNS depressants	May see additive central nervous system depressant effects.
Antacids	Decreased rate, but not extent of benzodiazepine absorption.
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.
Digoxin	Increased levels of digoxin seen with diazepam. Monitor for symptoms of toxicity.
Fluvoxamine	Increases in serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Nefazodone	Increased serum concentrations and effects of the benzodiazepines.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increases in benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives.
Protease inhibitors	Increases in levels of benzodiazepines metabolized by oxidation expected. Chlorazepate should not be used in patients on ritonavir. Choice of an agent metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Diazepam (Valium®) [1,4,8,10,13-16]

Criteria	Rationale

Usual dose range per day	**Tablets:** Adults-Two to 10 mg po qid. Alcohol withdrawal symptoms: Initial dosing 10 mg po qid. Taper as symptoms decrease. Geriatric patients-starting therapy at half the adult dose is recommended. Children- **Capsules:** Patients stabilized on doses of 15 mg or more per day may be converted to diazepam sustained release capsules in the same daily dose given every 24 hours. **Injection (adults):** Anxiety and panic disorders: 2 mg to 10 mg IM or IV repeated every 4 to 6 hours. Pre-operative anxiety or conscious sedation for procedures: 5 to 20 mg titrated as necessary. Treatment of status epilepticus: 5 to 10 mg at 10 to 15 minute intervals up to 30 mg. May repeat in 2 to 4 hours as necessary. **Injection (children):** Infants over 30 days, 1 to 2 mg repeated every 3 to 4 hours prn. Children 5 years and older-5 to 10 mg repeated every 3 to 4 hours prn. Treatment of status epilepticus: Infants over 30 days, 0.2 mg to 0.5 mg every 2 to 5 minutes up to a maximum of 5 mg IV. Children over 5 years of age-1 mg every 2 to 5 minutes to a maximum of 10 mg. **Rectal gel:** Mg/kg dose determined dependent upon the patient's age. It is recommended that the gel not be used more than 5 episodes per month and no more than 1 episode every 5 days.	Supported by product labeling and clinical practice.

Indication for use	**Labeled uses**: Management of anxiety disorders or short-term treatment of the symptoms of anxiety. For the symptomatic treatment of acute alcohol withdrawal. Skeletal muscle relaxation in spasticity disorders or spinal cord injury patients. Treatment of tetany. Treatment of status epilepticus. Adjunct therapy of seizure disorders. Management of preoperative anxiety, apprehension. **Unlabeled uses:** Treatment of panic disorder. Treatment of tension headache. Treatment of tremor.	Supported by product labeling and clinical practice.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.

Diazepam (continued)

Drug-drug interactions	
Alcohol/CNS depressants	May see additive central nervous system depressant effects.
Antacids	Decreased rate, but not extent of benzodiazepine absorption.
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.
Digoxin	Increased levels of digoxin in patients on diazepam. Monitor for symptoms of digoxin toxicity.
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with diazepam. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.

Nefazodone	May see increased serum concentrations and effects of the benzodiazepines.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives.
Protease inhibitors	Increases in levels of benzodiazepines metabolized by oxidation expected. Diazepam should not be used in patients on ritonavir. Choice of an agent metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Estazolam (Prosom®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	0.5 mg to 2 mg po hs	Clinical trials found estazolam superior to placebo in sleep induction and maintenance. Lower doses were less effective than the 2 mg dose, especially in sleep induction.
Indication for use	**Labeled use:** Treatment of	Clinical trials showed improvement in

	short-term insomnia.	sleep patterns for up to 12 weeks in adult patients.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.

Drug-drug interactions	
Alcohol/CNS depressants	May see additive central nervous system depressant effects.
Antacids	Decreased rate, but not extent of benzodiazepine absorption.
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.
Digoxin	Increased levels of digoxin in patients given diazepam. Monitor for symptoms of toxicity.
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Nefazodone	May see increased serum concentrations and effects of the benzodiazepines.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives.
Protease inhibitors	Increases in levels of benzodiazepines metabolized by oxidation expected. Estazolam should not be used in patients on ritonavir. Choice of an agent metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.

Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Flurazepam (Dalmane®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	15 to 30 mg po at bedtime	Doses used in controlled sleep studies.
Indication for use	Treatment of short-term insomnia, characterized by difficulty falling asleep, frequent nocturnal awakenings and/or early morning wakening.	Controlled studies in sleep laboratories have demonstrated positive results in objective and subjective symptoms of sleep induction and maintenance.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.	
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.	
Digoxin	Increased levels of digoxin in patients taking diazepam. Monitor for symptoms of toxicity.	
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.	
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.	
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.	
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.	
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.	

Nefazodone	May see increased serum concentrations and effects of the benzodiazepines.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives was observed.
Protease inhibitors	Increases in levels of benzodiazepines metabolized by oxidation expected. Flurazepam should not be used in patients on ritonavir. Choice of an agent metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Halezepam (Praxipam®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	80 to 160 mg	Dosages used in short term trials. Comparable effect to chlorazepate 15 to 30 mg.
Indication for use	Management of anxiety disorders or short-term treatment of the symptoms of anxiety.	In short term trials, compared with placebo, patients on halazepam had significant improvement in anxiety symptom scores. Responses to halazepam were comparable to those with chlorazepate and superior to placebo.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.

Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.	
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.	
Digoxin	Increased levels of digoxin in patients taking diazepam. Monitor for symptoms of toxicity.	
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.	
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.	
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.	
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.	
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.	
Nefazodone	May see increased serum concentrations and effects of the benzodiazepines.	
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives was observed.	
Protease inhibitors	Increases in levels of benzodiazepines undergoing oxidative metabolism expected. Halazepam should not be used in patients on ritonavir. Choice of an agent metabolized by conjugation is recommended.	
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.	
Drug-disease interactions		
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.	
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.	
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.	

Lorazepam (Ativan®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	1 to 10 mg po 2 to 12 mg IM or IV	Product labeling. Dosage range varied based on indication and patient tolerance.
Indication for use	**Labeled uses:** Management of anxiety disorders or short-term treatment of the symptoms of anxiety. Preoperative sedation to decrease anxiety, apprehension and recall. Treatment of status epilepticus. **Unlabeled uses:** Chemotherapy induced nausea and vomiting. Acute alcohol withdrawal. Psychogenic Catatonia. Chronic insomnia.	Comparative studies with other anxiolytic substances, such as antidepressants, ?-blockers, and neuroleptics, have demonstrated the greater efficacy of benzodiazepines. Lorazepam has been shown to have anti-panic effects similar to alprazolam at adequate doses. Controlled studies in sleep laboratories have demonstrated positive results. Product labeling, small comparison studies and widespread clinical use support the suitability of lorazepam for the listed indications.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.	
Digoxin	Increased levels of digoxin in patients taking diazepam. Monitor for symptoms of toxicity.	
Probenecid	Increased half-life of benzodiazepines undergoing oxidation metabolism.	
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.	
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.	
Drug-disease interactions		

Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Midazolam (Versed®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	Midazolam is titrated to effect with doses varying from 0.2 to 200 mg for intravenous midazolam. Use of oral midazolam is generally limited to preoperative sedation in children. Usual doses are 3 to 20 mg.	Dosage needs to be individualized, and response to midazolam varies widely.
Indication for use	Labeled uses: Preoperative sedation, conscious sedation prior to diagnostic or radiological procedures. Induction of general anesthesia. Unlabeled uses: Treatment of anxiety. Treatment of status epilepticus.	According to product labeling. Extensive clinical use as a sedative prior to short surgical procedures and as an adjunct in general anesthesia. Several case reports of successful treatment of refractory status epilepticus.
Duration of therapy	Duration of therapy must be individualized for each patient.	Because of the short duration of action and potential for serious respiratory depression, midazolam is indicated for acute therapy in monitored settings. For most indications, a single dose is appropriate.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.

Drug-drug interactions	
Alcohol/CNS depressants	May see additive central nervous system depressant effects.
Antacids	Decreased rate, but not extent of benzodiazepine absorption.
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.
Digoxin	Increased levels of digoxin. Monitor for symptoms of toxicity.
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Nefazodone	May see increased serum concentrations and effects of the benzodiazepines.
NNRTIs	Increases in serum concentrations and toxic reactions may be seen with delavirdine and effivirenz, especially in patients on oral midazolam. Use with extreme caution.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives.
Protease inhibitors	Increases in levels of midazolam and serious toxic effects have been reported. Use of midazolam in patients on protease inhibitors is contraindicated.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Oxazepam (Serax®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	15 to 180 mg	Product labeling. Recommended doses similar to those used in clinical trials with oxazepam.
Indication for use	**Labeled uses:** Management of anxiety disorders. Short-term therapy of the symptoms of anxiety. Anxiety related to depression. For the symptomatic treatment of acute alcohol withdrawal. Adjunctive agent in the treatment of partial seizures.	Numerous studies have confirmed the efficacy of oxazepam in the treatment of anxiety disorders and anxiety disorders with depression. Oxazepam had effects similar to alprazolam and buspirone. Oxazepam has comparable effects to other benzodiazepines in reducing sleep latency and decreasing frequent wakening in patients with insomnia. Decreased symptoms of severe alcohol withdrawal and decreased delirium were seen inpatients given oxazepam.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.	
Digoxin	Increased levels of digoxin in patients on diazepam. Monitor for symptoms of toxicity.	
Probenecid	Increased half-life of benzodiazepines undergoing oxidation metabolism.	
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.	
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.	
Drug-disease interactions		
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.	
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.	

Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Quazepam (Doral®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	7.5 to 15 mg	Product labeling. Doses up to 30 mg per day used in clinical trials. Greater effect was seen on the second and subsequent nights of therapy. This may be a result of quazepam's long half-life.
Indication for use	Treatment of insomnia.	Treatment effects superior to placebo and similar to flurazepam. Improvements in sleep patterns comparable to temazepam and triazolam with less rebound insomnia on discontinuation of therapy.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	

Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.
Azole antifungal agents	Decreased oxidative metabolism of the benzodiazepines. May see increases in benzodiazepine serum concentrations up to 200%.
Digoxin	Increased levels of digoxin in patients taking diazepam. Monitor for symptoms of toxicity.
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.
Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Nefazodone	May see increased serum concentrations and effects of the benzodiazepines.
Protease inhibitors	Increases in levels of quazepam and its active metabolites expected. Choice of an agent metabolized by conjugation is recommended.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Temazepam (Restoril®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per Day	15 to 30 mg	Product labeling. Doses of 15 to 30 mg were used in comparison studies.

Indication for use	**Labeled uses:** Short term treatment of insomnia. **Unlabeled uses:** Treatment of anxiety and panic attacks.	Decreased latency and wakening when compared with placebo in the short term treatment of insomnia. Similar effects to flurazepam with less morning sleepiness. Effects similar to lorazepam and oxazepam for insomnia and as a preoperative medication.
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.	
Digoxin	Increased levels of digoxin in patients taking diazepam. Monitor for symptoms of toxicity.	
Probenecid	Increased half-life of benzodiazepines undergoing oxidation metabolism.	
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.	
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.	
Drug-disease interactions		
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.	
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.	
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.	

Triazolam (Halcion®) [1,4,8,10,13-16]

Criteria		Rationale
Usual dose range per day	0.125 to 0.5 mg	Dose used in comparisons and extensive clinical practice.
Indication for use	**Uses:** Short term treatment of insomnia. Pre-surgery sedative.	Controlled studies in sleep laboratories have demonstrated positive results. Widespread clinical use
Duration of therapy	Duration of therapy must be individualized for each patient.	No strong evidence for an optimal duration of therapy is available.
Duplicity of therapy	In general, two or more benzodiazepines should not be used together.	The pharmacological properties of the benzodiazepines are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antacids	Decreased rate, but not extent of benzodiazepine absorption.	
Anticonvulsants	Interactions varied. May see increased or decreased effects of the anticonvulsant and/or the benzodiazepine. Monitor for decreased and toxic effects.	
Azole antifungal agents	Increases in AUC of 27 fold were seen with triazolam after single doses of ketoconazole or itraconazole. Concurrent use is contraindicated. Lesser, but significant increases expected with fluconazole. Use of an alternative agent is recommended.	
Digoxin	Increased levels of digoxin seen in patients taking diazepam. Monitor for symptoms of toxicity.	
Fluvoxamine	Increased serum concentrations by 75 to 150% reported with similar benzodiazepines. May see increased benzodiazepine effects.	
Levodopa	Decreased effectiveness of levodopa in treating Parkinson's disease.	
Macrolide antibiotics	Decreased metabolism by erythromycin and clarithromycin. May see increased effects of benzodiazepine. Effect not seen with azithromycin.	
Methylxanthines	Reversal of the sedative effects of the benzodiazepines.	

Miscellaneous inhibitors of oxidative metabolism	Decreases in clearance of benzodiazepines undergoing oxidative metabolism by 30% to 50%. May see increased benzodiazepine effects.
Nefazodone	Increased serum concentrations by approximately 400%. Decrease triazolam dose by 75%.
NNRTIs	Significant Increases in serum concentrations and toxic reactions have been reported delavirdine and effivirenz. Concurrent use is not recommended. Other NNRTIs do not affect triazolam concentrations.
Oral contraceptives	Inhibit oxidative metabolism of benzodiazepines. Increased benzodiazepine half-life by 50% to 100% in women taking low dose oral contraceptives.
Protease inhibitors	Increases in triazolam serum concentrations and toxic effects noted with all of the protease inhibitors. Concurrent use is contraindicated.
Rifamycins	Increased metabolism of benzodiazepines by induction of the CYP450 enzyme system. Use of a benzodiazepine metabolized by conjugation is recommended.
Drug-disease interactions	
Glaucoma	Benzodiazepines are contraindicated in patients with narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma well-controlled with medication.
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.
Pregnancy	Chronic use of benzodiazepines should be avoided when possible in patients who are pregnant.

Zaleplon (Sonata®)[5,9,10]

Criteria		Rationale
Usual dose range per day	5 to 20 mg	Product labeling
Indication for use	Short term treatment of insomnia	Product labeling. Several small trials found zaleplon as effective as triazolam in decreasing sleep latency.
Duration of therapy	Must be individualized for each patient. Zaleplon should not be prescribed in quantities exceeding 1-month supply.	Product labeling. Zaleplon used for up to 28 days without development of tolerance in clinical trials.
Duplicity of therapy	In general, two or more benzodiazepine agonists should not be used together.	The pharmacological properties of the benzodiazepine agonists are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		

Alcohol/CNS depressants	May see additive central nervous system depressant effects.
Cimetidine	An inhibitor of both CYP450 3A and aldehyde dehydrogenase produced an 85% increase in AUC of zaleplon. Lower initial doses (5 mg) of zaleplon are recommended in patients taking cimetidine.
Diphenhydramine	An inhibitor of aldehyde dehydrogenase, had no effect on zaleplon pharmacokinetics.
Rifampin	The Cmax and AUC of zaleplon was decreased by approximately 85% in patients taking rifampin.
Warfarin	Zaleplon did not alter the pharmacokinetics or PT in patients taking warfarin.
Drug-disease interactions	
Pregnancy	The effects of zaleplon have not been studied in patients who are pregnant. Use of zaleplon is not recommended in pregnant women.

Zolpidem (Ambien®)[6-8,10,12,14-16]

Criteria		Rationale
Usual dose range per day	5 to 10 mg	Product labeling.
Indication for use	**Labeled use:** short-term treatment of insomnia **Unlabeled uses:** pre-operative sedation Supranuclear palsy	Product labeling. Effective in decreasing sleep latency and nocturnal awakenings compared with placebo. Zolpidem found superior to placebo in producing pre-operative sedation in a small group of patients. Zolpidem increased voluntary eye movement in a small group of patients with supranuclear palsy, compared with placebo and carbidopa-levodopa.
Duration of therapy	Must be individualized for each patient. Reevaluation of therapy continued for more than 7 to 10 days is recommended.	Product labeling. Used up to twelve weeks in clinical trials.
Duplicity of therapy	In general, two or more benzodiazepine agonists should not be used together.	The pharmacological properties of the benzodiazepine agonists are similar. A second agent is not expected to increase efficacy.
Drug-drug interactions		
Alcohol/CNS depressants	May see additive central nervous system depressant effects.	
Antidepressant agents	Reports of nightmares, hallucinations and delusions have been reported. Most patients had several risk factors for increased zolpidem serum concentrations.	
Azole antifungal agents	Decreased oxidative metabolism of zolpidem. Ketoconazole increased zolpidem serum concentrations by approximately 30% in one group. Fluconazole and itraconazole did not significantly impair the metabolism of zolpidem.	
Cimetidine, Ranitidine	No pharmacokinetic or pharmacodynamic changes in zolpidem were seen in patients taking cimetidine or ranitidine.	
Rifampin	Decreased AUC and Cmax of zolpidem of 27% and 58%, respectively were noted in subjects treated with rifampin for 5 days prior to taking zolpidem.	
Warfarin	Zolpidem did not affect the PT in patients taking warfarin.	
Drug-disease interactions		
Hypoalbuminemia	Increased concentration of unbound (active) drug. Increased benzodiazepine effects may be seen.	
Pregnancy	The effects of zolpidem have not been studied in patients who are pregnant. Use of zolpidem is not recommended in pregnant women.	

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Drug List Appendix[8,10,13,14]

Central Nervous System Depressants

Barbiturates

Amobarbital
Mephobarbital
Pentobarbital
Secobarbital

Opiates

Codeine
Hydrocodone
Hydromorphone
Levorphanol
Meperidine
Methadone
Morphine
Opium Tincture
Oxycodone
Oxymorphone
Paregoric
Pentazocine
Propoxyphene

Miscellaneous CNS depressants

Chloral hydrate
Diphenhydramine
Ethchlorvynol
Haloperidol
Hydroxyzine
Promethazine
Zolpidem

Antacids

Aluminum hydroxide
Magnesium hydroxide

Anticonvulsants

Divalproex
Gabapentin
Phenytoin
Phenobarbital

Antidepressants
Bupropion
Desipramine
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Trazodone
Venlafaxine.

Azole antifungal agents
Fluconazole
Itraconazole
Ketoconazole

Macrolide antibiotics
Azithromycin
Clarithromycin
Erythromycin

Methylxanthines
Caffeine
Theophylline

Miscellaneous inhibitors of oxidative metabolism
Cimetidine
Disulfiram
Diltiazem
Fluoxetine
Isoniazid
Verapamil

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) with effects on benzodiazepines
Delavirdine
Effiravenz

Oral combination contraceptives
Ethinyl estradiol and desogestrel
Ethinyl estradiol and ethynodiol diacetate
Ethinyl estradiol and levonorgestrel

Ethinyl estradiol and norgestimate
Ethinyl estradiol and norethindrone
Ethinyl estradiol and norgestrel
Mestranol and norethindrone

Oral estrogen products
Chlorotrianisene
Diethylstilbestrol
Estradiol
Estradiol and testosterone
Estrogens, conjugated
Estrogens, esterified
Estrogens and medroxyprogesterone
Estrogens and methyltestosterone
Estrone
Ethinyl Estradiol
Ethinyl Estradiol and ethynodiol diacetate
Ethinyl Estradiol and levonorgestrel
Ethinyl Estradiol and norethindrone
Ethinyl Estradiol and norgestrel
Mestranol and norethindrone
Polyestradiol

Protease inhibitors
Amprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Rifamycins
Rifampin
Rifabutin

Table 1. Benzodiazepines-pharmacokinetic properties[1,4-6,8,10]

Drug	Onset after oral administration	Protein Binding	Elimination half-life (hours)	Active metabolites*	Major pathway of metabolism	Cytochorme P450 Isoenzymes Involved in Metabolism
Alprazolam	Intermediate	80%	12 to 15	Insignificant	Oxidation	CYP3A3/4
Chlordiazepoxide	Intermediate	90 to 98%	5 to 30	Desmethylchlordiaze-poxide Demoxepam	Oxidation	Not identified
Clonazepam	Fast	85%	18 to 50	Insignificant	Oxidation	CYP3A3/4
Clorazepate Dipotassium	Intermediate	80 to 95%	Not significant	Desmethyldiazepam	Oxidation	CYP2C19
Diazepam	Very fast	98%	20 to 80	Desmethyldiazepam	Oxidation	CYP1A2,2C8, 2C9,2C19 (major) CYP3A3/4 (minor)
Estazolam	Intermediate	93%	10 to 30	Insignificant	Oxidation	Not identified
Flurazepam Hydrochloride	Fast	97%	40 to 114	Desalkylflurazepam	Oxidation	Not identified
Halazepam	Slow		Not significant	Desmethyldiazepam	Oxidation	CYP2C19
Lorazepam	Intermediate	85 to 92%	10 to 20	None	Conjugation	None
Midazolam	Very Fast	95 to 99%	2 to 5	None	Oxidation	CYP3A3/4
Oxazepam	Slow	86 to 96%	5 to 20	None	Conjugation	None
Quazepam	Fast	95 to 99%	25 to 40	2-oxoquazepam, desalkyloxoquazepam	Oxidation	CP4503A, 2C
Temazepam	Intermediate	96%	10 to 20	Insignificant	Conjugation	None
Triazolam	Intermediate	89 to 94%	1.5 to 5	Insignificant	Oxidation	CYP3A3/4, 3A5-7
Zaleplon	Very Fast	60%	1	None	Oxidation	Aldehyde oxidase, CYP3A4
Zolpidem	Fast	92%	2.5	None	Oxidation Hydroxylation	

? The active metabolite desmethyldiazepam has a half-life in adults of 60 to 120 hours, demoxepam 14 to 119 hours, desalkylflurazepam 47 to 100 hours, quazepam's metabolites 40 to 110 hours. This can extend the effects of a benzodiazepine with a relatively short half-life and account for cumulative adverse effects.